Published in final edited form as:

Tetrahedron Lett. 2012 February 29; 53(9): 1051–1055. doi:10.1016/j.tetlet.2011.12.062.

Synthesis and cross-coupling reactions of imidomethyltrifluoroborates with aryl chlorides

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Abstract

Potassium imidomethyltrifluoroborate salts were efficiently synthesized. Potassium phthalimidomethyl-trifluoroborate was successfully used in Suzuki–Miyaura-like cross-coupling reactions with a variety of aryl chlorides.

Keywords

Potassium imidomethyltrifluoroborates; Suzuki–Miyaura cross-coupling reaction; *N*-Benzylphthalimides

Certain imides, particularly phthalimide derivatives, are biologically active as TXA₂ receptor antagonists,^{1a} analgesics,^{1b} anti-inflammatory agents,^{1c,d} anticonvulsants,^{1e} herbicides,^{1f} insecticides,^{1g} and antipsychotics.^{1h} *N*-Benzylphthalimides have been found to exhibit non-nucleoside HIV-1 reverse transcriptase inhibitor activities² and TPA induced TNF- α -production enhancing activity by human leukemia HL-60 cells.³ This large array of biological activities makes imido derivatives desirable target molecules for synthesis. In addition, *N*-benzylphthalimides are well known for the aminomethylation of aromatic substrates⁴ and have been used for the synthesis of anti HIV compounds.^{4a} Traditional synthetic approaches to these imides have involved formation of the carbon–nitrogen bond via *N*-benzylation of phthalimides proceeding via S_N2 reactions of benzyl halides with phthalimide (or potassium phthalimide),^{1a,5} or the Mitsunobu reaction⁶ of phthalimide and benzyl alcohols (Scheme 1, a).

A complementary synthetic approach can be envisaged by forming the carbon–carbon bond via a Suzuki–Miyaura cross-coupling (Scheme 1, b). This new disconnection would provide several advantages. The first is that the Suzuki–Miyaura cross-coupling reaction is an extremely versatile C–C bond forming reaction in organic synthesis.⁷ Traditionally, boronic acids or boronate esters are used in Suzuki–Miyaura coupling reactions. However, both suffer from limitations owing to the difficulty in purification, air and moisture sensitivity, and in particular the sensitivities of boronic acids to protodeboronation. As an alternative to boronic acids and boronate esters, organotrifluoroborate salts have proven to be stable and

efficient coupling partners in Suzuki–Miyaura coupling reactions.⁸ We have previously reported the synthesis and use of various organotrifluoroborates in cross-coupling reactions. 8b,c,⁹ Most recently, the synthesis and cross-coupling reactions of various functionalized organomethyltrifluoroborates such as sulfonamidomethyl, amidomethyl, ammoniomethyl, and alkoxymethyltrifluoroborates have been reported.¹⁰ Coupling reactions with these organotrifluoroborates have proven to be tolerant of a variety of embedded functional groups. A second advantage is that a much larger library of aryl chlorides (compared to benzyl chlorides) is commercially available, thus adding increased scope and diversity to potential applications of this new synthetic approach (Scheme 1, b).

Herein, we report the efficient synthesis¹¹ of potassium phthalimidomethyltrifluoroborate (**3a**) and potassium succinimidomethyltrifluoroborate (**3b**) and a new imidomethylation procedure resulting from cross-coupling reactions of potassium phthalimidomethyltrifluoroborate with a variety of aryl chlorides.

After numerous attempts under various reaction conditions, the imidomethyltrifluoroborates **3a** and **3b** were optimally prepared using a synthetic route based on Matteson's chemistry.¹² Treatment of phthalimide (**1a**) and succinimide (**1b**), respectively, with potassium hydride in the presence of bromomethylpinacolboronate (**2**) in THF/DMF at room temperature for 24 h gave the corresponding crude boronate esters, which were directly treated with potassium hydrogen fluoride for 1 h to afford, after isolation and purification,¹³ the desired potassium phthalimidomethyltrifluoroborate (**3a**, 60%) and potassium succinimidomethyltrifluoroborate (**3b**, 80%) (Scheme 2).

After successful synthesis of potassium phthalimidomethyltrifluoroborate (**3a**), cross-coupling reaction conditions were screened and optimized using 4-chloroanisole (**4a**) as the electrophilic partner. These optimization studies involved using different catalysts, ligands (Fig. 1), bases, and solvent systems at different temperatures (Table 1). The coupling product was first observed at 100 °C using PdCl₂(MeCN)₂ or PdCl₂(PhCN)₂ as the palladium source in 40–43% conversion (Table 1, entries 5 and 6). By replacing Cs₂CO₃ base with K₂CO₃ the percent conversion increased from 40–43% to 85% (56% yield) (Table 1, entry 7). Even for a proven catalyst–ligand system, the ratio of *t*-BuOH/H₂O in the solvent system had a profound effect on product formation (Table 1, entries 7–9). Similarly, for a proven catalyst–ligand system, changes in base (Table 1, entries 10 and 11) and/or solvent systems (Table 1, entries 12–16) had dramatic effects on the coupling reaction. For a 20 h reaction time, increasing the catalyst/ligand loading from 2.5 mol %/5 mol % to 10 mol %/20 mol % increased the conversion from 32% to 100% (Table 1, entries 17–19). Adequate amounts (3 equiv) of base were also essential for efficient coupling (Table 1, entry 20). Entries 21–28 demonstrate the significant role of ligand selection in that by varying only the ligand (Fig. 1), the percent conversions range from a trace to 77%. Ultimately, the optimized conditions resulted in 100% conversion and a 64% isolated yield (Table 1, entry 29) when using PdCl₂(MeCN)₂ (7.5 mol %), X-Phos (15 mol %), K₂CO₃, in *t*-BuOH/H₂O (4:1) for 13 h at 100 °C. To our surprise, when trifluoroborate **3a** was treated with 4-chloroanisole (**4a**) under these optimized reaction conditions, but substituting microwave heating for conventional heating, only a trace amount of cross-coupled product was observed. Also, the succinimidomethyltrifluoroborate (**3b**) when treated with 4-chloroanisole (**4a**) did not afford any crosscoupled product under these reaction conditions.

These optimal conditions were then used with an array of diversely substituted aryl chlorides to explore the scope of the reaction (Table 2). The coupling products **5b–5j** were formed in 36–77% yields. Functional group tolerance included methoxy, ester, ketone, and pyrrole units. In contrast, 4-chloroaniline and 2-chloro-5-methylphenol were not tolerated and yielded no cross-coupling product, presumably due to the role of the free hydroxy and amino

functional groups. The yields in Table 2 indicate no clear structure-reactivity correlation with the aryl chloride variables of steric hindrance or electrophilicity. Reaction times beyond the minimum reaction time required for 100% conversion (based on TLC monitoring of the aryl chloride) often led to reduced isolated yields. This observation is consistent with product decomposition under the reaction conditions and highlights the need to avoid excessive reaction times.

The heteroaryl chloride **4k** afforded the cross-coupled product **5k** in 35% yield (Table 2, entry 10). However, under the same reaction conditions, a variety of substituted pyridine, quinoline, and thiophene heteroaryl chlorides resulted in unwanted reduction of the heteroaryl chlorides, while producing only traces of the desired cross-coupling products.

Trifluoroborate **3a** was shown to couple with a variety of electrophiles (Table 3). Coupling with bromobenzene and iodobenzene produced 43% and 7% yields, respectively (Table 3, entries 2 and 3). Phenyl triflate, phenyl tosylate, and phenyl mesylate afforded 36%, 31%, and 48% yields of cross-coupled products, respectively (Table 3, entries 4–6).

In summary, potassium succinimidomethyltrifluoroborate and potassium phthalimidomethyltrifluoroborate salts were successfully synthesized from succinimide and phthalimide, respectively, in moderate to good yields. As a new approach to aminomethylation methods, potassium phthalimidomethyltrifluoroborate was successfully used in Suzuki–Miyaura-like cross-coupling reactions with a variety of aryl chlorides and one heteroaryl chloride.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by a National Priorities Research Program (NPRP) grant from the Qatar National Research Fund (Grant No. 08-035-1-008). G.A.M. thanks the National Institute of General Medical Sciences for support.

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13. See the Supplementary data for complete experimental procedures.

Figure 1.
Structures of the various phosphine ligands.

Scheme 1.
Retrosynthetic analysis.

Scheme 2.
Synthesis of potassium imidomethyltrifluoroborates.

Table 1

Cross-coupling of **3a** with 4-chloroanisole (**4a**): optimization studies

Entry	Catalyst/mol %	Ligand/mol %	Base	Solvent/ratio	T (LC)	Time (h)	Conversion (yield %) ^a
1	Pd(OAc) ₂ /5	XPhos/10	CS ₂ CO ₃	CPME:H ₂ O/10:1	85	24	0
2	Pd(dppf) ₂ /5	XPhos/10	CS ₂ CO ₃	CPME:H ₂ O/10:1	85	24	0
3	Pd(PPh ₃) ₄ /5	XPhos/10	CS ₂ CO ₃	CPME:H ₂ O/10:1	85	24	0
4	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	80	24	0
5	PdCl ₂ (MeCN) ₂ /5	XPhos/10	CS ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	20	43
6	PdCl ₂ (PhCN) ₂ /5	XPhos/10	CS ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	20	40
7	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	16	85 (56)
8	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/8:1	100	16	0
9	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/2:1	100	16	20
10	PdCl ₂ (MeCN) ₂ /5	XPhos/10	<i>t</i> -BuONa	<i>t</i> -BuOH:H ₂ O/4:1	100	20	5
11	PdCl ₂ (MeCN) ₂ /5	XPhos/10	DIPEA	<i>t</i> -BuOH:H ₂ O/4:1	100	25	Trace
12	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	DMSO:H ₂ O/4:1	100	16	0
13	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	DMF:H ₂ O/4:1	100	16	0
14	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	CPME:H ₂ O/4:1	100	16	2
15	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	Toluene:H ₂ O/4:1	100	16	0
16	PdCl ₂ (MeCN) ₂ /5	XPhos/10	K ₂ CO ₃	CH ₃ CN:H ₂ O/4:1	100	16	0
17	PdCl ₂ (MeCN) ₂ /2.5	XPhos/5	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	20	32
18	PdCl ₂ (MeCN) ₂ /5	XPhos/7.5	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	20	46
19	PdCl ₂ (MeCN) ₂ /10	XPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	20	100 (58)
20	PdCl ₂ (MeCN) ₂ /10	XPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	20	60 ^b
21	PdCl ₂ (MeCN) ₂ /10	RuPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	77
22	PdCl ₂ (MeCN) ₂ /10	DavePhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	16
23	PdCl ₂ (MeCN) ₂ /10	MePhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	42

Entry	Catalyst/mol %	Ligand/mol %	Base	Solvent/ratio	T (LC)	Time (h)	Conversion (yield %) ^a
24	PdCl ₂ (MeCN) ₂ /10	<i>t</i> -Bu-XPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	6
25	PdCl ₂ (MeCN) ₂ /10	SPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	47
26	PdCl ₂ (MeCN) ₂ /10	DPEPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	Trace
27	PdCl ₂ (MeCN) ₂ /10	JohnPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	12
28	PdCl ₂ (MeCN) ₂ /10	BrettPhos/20	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	24	1
29	PdCl ₂ (MeCN) ₂ /7.5	XPhos/15	K ₂ CO ₃	<i>t</i> -BuOH:H ₂ O/4:1	100	13	100 (64)

^a Reagents and conditions: 1.0 equiv of aryl chloride, 1.2 equiv of trifluoroborate **3a**, conversion measured by GC/MS on the crude product mixture based on 4-chloro-anisole; all reactions were carried out overnight (13–24 h); isolated yields after silica gel column chromatography; CPME = cyclopentyl methyl ether.

^b Two equivalents of base were used.

Table 2Cross-coupling of **3a** with aryl and heteroaryl chlorides

Reaction scheme: **3a** + (Het)Ar-Cl (**4**) $\xrightarrow[\text{100 } ^\circ\text{C.}]{\text{PdCl}_2(\text{MeCN})_2 \text{ (7.5 mol\%)}, \text{X-Phos (15 mol\%)}, \text{K}_2\text{CO}_3 \text{ (3 equiv)}, \text{t-BuOH/H}_2\text{O (4/1; 0.25 M)}}$ **5** (Ar(Het))

Entry	(Het)Ar-Cl	Time/h	Product 5^a (%)
1	4b	42	5b (36)
2	4c	14	5c (58)
3	4d	14	5d (77)
4	4e	14	5e (71)
5	4f	14	5f (46)
6	4g	6	5g (51)
7	4h	5	5h (56)
8	4i	15	5i (74)
9	4j	18	5j (61)
10	4k	15	5k (35)

^aReagents and conditions: 1.0 equiv of aryl or heteroaryl chloride, 1.2 equiv of trifluoroborate **3a**; isolated yields after silica gel column chromatography.

Table 3

Electrophile compatibility

Entry	X	Time/h	Yield ^a (%)
1	Cl	14	58
2	Br	18	43
3	I	17	7
4	OTf	17	36
5	OTs	18	31
6	OMs	17	48

^a Reagents and conditions: 1.0 equiv of ArX; 1.2 equiv of trifluoroborate **3a**; isolated yields after silica gel column chromatography.